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Universiteit Leiden



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Title: Multi-biomarker pharmacokinetic-pharmacodynamic relationships of central nervous systems active dopaminergic drugs

Issue Date: 2018-11-21

Propositions to the thesis

'Multi-Biomarker PK/PD Relationships of CNS Active Dopaminergic Drugs'

1. Even selective drugs may perturb multiple biochemical pathways, urging the need for multi-biomarker approaches over single-biomarker approaches. *This thesis*
2. Both affinity and signal transduction efficiency may explain differences with regard to *in vivo* potency among biomarkers. By integrating pharmacological knowledge into a multi-biomarker PK/PD approach it becomes possible to separate these two underlying factors. *This thesis*
3. CNS biomarker discovery needs a combination of serial plasma sampling, intracerebral microdialysis, PK/PD modeling and time-dependent multivariate pharmacometabolomics data analysis. *This thesis*
4. Neurotransmitter levels in the blood (or plasma) may not necessarily be a good biomarker of pharmacological effects in the brain. *This thesis*
5. Biochemical phenotyping provides a functional characterization of CNS drugs that is an accurate reflection of their efficacy profile. (*A. Carlsson et al. Ann. Rev. Pharmacol. Toxicol., 2001*)
6. The quantitative and integrative analysis of target site drug concentrations, target binding and target activation increases the success rates in early drug development dramatically. (*P. Morgan et al., Drug Discov. Today, 2012*)
7. Pharmacometabolomics is a straightforward approach to discover system-wide biochemical biomarkers of drug effects. It can be applied in a non-invasive manner via plasma sampling; it captures genomic, proteomic and environmental influences; and the costs are relatively low. (*T. Burt & S. Nandal, Clin. Transl. Sci., 2016*)
8. Rats and mice are not small humans, however, many biochemical pathways overlap. Qualitative and quantitative characterization of pharmacokinetics in relation to these pathways is essential for a proper translation of drug effects between species. (*Based on E.M. Blais et al., Nat. Comm., 2017; M. Danhof et al., Tr. Pharmacol. Sci., 2008*)
9. 'It is a capital mistake to theorise before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.' (*Sir Arthur Conan Doyle, Sherlock Holmes – The complete illustrated short stories, Chancellor Press, 1985, p.6*)
10. A sustainable way of life is too much seen as only a preference of a small group of people, while the urgency of climate change requires an effort from all of us.
11. Philosophy of Science should be a mandatory course in the academic education of Life Sciences.
12. 'Let food be thy medicine and medicine be thy food.' *Often wrongly attributed to Hippocrates*

Willem van den Brink,
Leiden, 21 november 2018